UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/082,112	05/20/98	MENDOZA A	MSU4.1-406

HM12/1222

IAN C MCLEOD
2190 COMMONS PARKWAY
OKEMOS MI 48864

EXAMINER	
TURNER, S	
ART UNIT	**PAPER NUMBER**
1644	10

DATE MAILED: 12/22/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/082,112	Mendoza
Examiner	**Group Art Unit**
Sharon L. Turner, Ph.D.	1645

☒ Responsive to communication(s) filed on *10-8-99*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *16-27* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *16-27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

1. The amendments filed 10-8-99 has been entered into the record and has been fully considered.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

3. Rejection of claims 16-25 is withdrawn under 35 U.S.C. 112, first paragraph, in view of applicants amendments. The claims as amended are drawn to a mixture of proteins comprising mixed intracellular and mixed extracellular proteins of *P. insidiosum.*

4. Rejection of claims 16, and 18-19 is withdrawn under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

New Rejections Based on Amendment

The invention as amended is no longer drawn to a method comprising the administration of a composition comprising separated proteins but is drawn to a method comprising the administration of a composition comprising mixed intracellular and extracellular proteins.

5. Claims 16-22, and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Mendoza et al, Mycopathologica, 1992(a), 119:89-93, (IDS: Ref. AI).

Mendoza et al, 1992 teach two vaccines for Pythiosis. The first, page 90, column 2, Vaccine production, comprises inoculation and growth of *P. insidiosum* in Sabouraud dextrose

broth, followed by filtration through a Whatman No. 40 filter paper, claim. The fungal mass was then washed three times with 200 ml of 0.75% of NaCl solution. In the last wash, the cell-mass was resuspended in 15 ml of sterile saline solution and then broken in a Braum MSK cell homogenizer, until microscopically 80% of the hyphae were observed to have been fragmented. This step produces a mixture of proteins which include mixed intracellular and extracellular proteins from the cell material, thus providing an admixture of mixed intracellular and mixed extracellular proteins. The hyphae were transferred to a container, desicated and the final dose was adjusted to 5 mg dry weight/ml with 5% phenolized (an equivalent reagent to thimersol, see Merthiolate, J. Clin. Microbiol., Nov. 1992, p. 2980-83 (AJ)), in sterile saline (an aqueous) solution. Homogenization breaks cells open and thus inherently comprises the same mixture of intracellular and extracellular proteins provided by sonication. As described on page 89, column 1, line 12 Introduction, Mendoza et al., have found that nine Pythium strains isolated from humans, horses and dogs with active pythiosis belonged to the same species, teaching that *P. insidiosum* is inherently equivalent to ATCC 58643, (old claim 21). *P. insidiosum* 58643 was used in the production of the CMV vaccine, page 90, Vaccine production. Absent evidence to the contrary, the 58643 is inherently equivalent to the 74446 strain now claimed. The CMV procedure utilizes centrifugation for the cell washes, claim 24. The beneficial results of the CMV vaccine are illustrated in Tables 1-3. In addition to the CMV vaccine, the SCAV vaccine is prepared by growth in Sabouraud dextrose broth for 5 days, the cultures are then killed with phenol (0.5% final concentration), (an equivalent reagent to thimersol, see Merthiolate, J. Clin.

Microbiol., Nov. 1992, p. 2980-83 (AJ)), and then concentrated 20-fold in a stir cell. The concentrated soluble antigen obtained from each flask is precipitated with 50 ml of chilled acetone twice and centrifuged at 10,000Xg. The supernatant is drained and the precipitated antigen is resuspended in 25 ml 0.75% NaCl sterile solution, see p. 90, col. 2, line 33-p.91, col. 1, line 8. This preparation thus comprises mixed intracellular and mixed extracelluar proteins. Vaccination and results from vaccination are shown in Figures 1, 2, and 4. Both vaccines are administered to mammals subcutaneously, see, p. 91, col. 1, lines 16-20. The process limitations of claims 16-22 and 24-27 do not define over the mixture of the prior art reference comprising intracellular and extracellular proteins. The step of dialyzing the proteins.does not remove either all of the intracellular or all of the extracellular proteins.

6. Claims 16-22 and 24-27 are rejected under 35 U.S.C. 102(b) as being unpatentable over Mendoza et al, J. Mycol. Med, 1996, 6:151-164.

Mendoza et al, 1996 teach the prevalence of human pythiosis infection and a need for effective human vaccines, page 156, column 2. Mendoza et al, 1996, also teach the benefits of vaccination using antigens derived from *P. insidiosum*, see page 158, column 1, lines 5-8, 24 and Immunotherapy, page 161-162 with reference to the vaccine treatments of IDS:References AB, AC, AD, AH, AI and AJ. Mendoza et al, 1996, teach that the addition of cytoplasmic antigens, contining the 28K, 30K and 32K immunodominant proteins to the original pythium vaccine (Miller et al, SCAV vaccine and Mendoza et al, CMV vaccine) (in reference to Mendoza, Enhancement of the therapeutic effect of a vaccine against equine pythiosis insidiosis by a hyphal

antigen protein of the oomycete *Pythium insidiosum,* The Third NIAID Workshop in Medical Mycology Series. Montana, September, p.9, 1995) enhances curative properties, page 159, line 15-18. Thus, Mendoza et al teach a vaccine comprising mixed intracellular and extracellular proteins. The process limitations of claims 16-22 and 24-27 do not define over the mixture of the prior art reference comprising intracellular and extracellular proteins. The step of dialyzing the proteins.does not remove either all of the intracellular or all of the extracellular proteins.

7. Claims 23 and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Mendoza et al, Mycopathologica, 1992(a), 119:89-93, (IDS: Ref. AI) or Mendoza et al, J. Mycol. Med, 1996, 6:151-164 in view of Mendoza et al, J. Clin. Microbiology, Nov. 1992, p. 2980-83 and Panella et al, Cancer Res., 50(14):4429-35.

The benefit of mixed intracellular and extracellular protein vaccines are disclosed in Mendoza et al, Mycopathologica, 1992(a), 119:89-93, (IDS: Ref. AI) or Mendoza et al, J. Mycol. Med, 1996, 6:151-164 as set forth above. These vaccines however are not produced by the process steps outlined in claims 23 and 26-27, wherein the cells are killed with thimerosol and wherein the mixed proteins are dialyzed to remove low molecular weight components less than 10,000 MW.

Mendoza et al, J. Clin. Microbiology, Nov. 1992, p. 2980-83 teach the alternative preparation of antigens from *P. insidiosum*, wherein the cells are killed with Merthiolate™, the trademark of thimerosol, (Sodium ethyl-mercurithiosalicylate; Mercury[(o-carboxypphenyl)thio]ethyl sodium salt, see Sigma Catalog, 1992), and ultrafiltration under

positive pressure in a stirred cell fitted with a PM-10 membrane (Amicon Corp., Lexington, Mass.). These steps kill the cells, and remove the thimerosol from the vaccine as it exhibits effects on the immune response which are independent of the administered antigens, see for example Panella et al which teach the benefit of thimerosol as an antigenic preservative and the benefit of subsequent removal by dialysis to eliminate nonspecific immune effects of the ethyl-mercury (in favor of the antigens being tested). Thus, thimerosal is a reagent which provides an alternative method to arrive at a killed but immunogenicaly preserved composition. (The composition after dialyzing could loose very small proteins under 10,000 molecular weight but would not remove extracellular and intracellular proteins greater than 10,000 MW which are protective). Thus it would have been prima facie obvious to one of skill in the art (knowing the presence of protective high MW intracellular and extracellular proteins from P. insidiosum), to modify the killing step using phenol with a killing step using thimerosal (an antigenic preservative), and subsequent dialysis, to produce an antigenic composition with immunogenic properties of the antigenic preparations prepared with phenol. One of skill in the art would have motivation to use these steps to provide antigenic preparations based on the teachings of Panella et al of the preservative properties of thimerosol and the ability to remove the ethyl-mercury by dialysis. One of skill in the art would have expected at least equivalent results with such a preparation due to the killing and preservation of P. insidiosum antigenic epitopes and the elimination of nonspecific immunes stimulation by the ethyl-mercury.

8. The amendment filed 10-17-99 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: ATCC 74446.

Applicant is required to cancel the new matter in the reply to this Office action.

9. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Amendment of claim 21 removes ATCC 58643 and replaces it with ATCC 74446. Applicant has submitted no support for such amendments to the claim and no support is found in the specification as originally filed. Such recitation constitutes new matter.

Status of Claims

10. No claims are allowed.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

12. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995.

Sharon L. Turner, Ph.D.
December 17, 1999

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600